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Mini-Review

Slow and Steady Wins the Race: 25 Years Developing the GLP-1 Receptor as an Effective Target for Weight Loss

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Abstract

Recent evidence from clinical trials supports the efficacy and tolerability of glucagon-like peptide 1 (GLP-1) receptor agonists as useful agents for weight loss. Although originally developed as glucose lowering agents for people with type 2 diabetes, progress in research over the last 3 decades has demonstrated that GLP-1 receptor agonists act in the central nervous system to reduce food intake. This minireview summarizes key aspects of GLP-1 biology and the clinical studies supporting the utility of the GLP-1 receptor signaling system as a therapeutic target for weight loss.

Key Words: obesity, glucagon-like peptide 1, GLP-1 receptor agonists, weight loss

Abbreviations: CNS, central nervous system; fMRI, functional magnetic resonance imaging; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin A1c; PBO, placebo; T2DM, type 2 diabetes mellitus.

The seemingly inexorable rise in rates of obesity is a worldwide problem that constitutes one of the major public health challenges of the 21st century. Obesity and overweight confer a range of comorbidities that affect the quality and quantity of life for millions of people. Weight gain and requests for help with weight loss are among the most common concerns patients bring to endocrinologists, and these discussions are frequently difficult, given the lack of reliable options for weight loss. While dietary and lifestyle measures can be useful, success is difficult to maintain and the variety of prescribed strategies work for some, but demonstrably not most, people. Bariatric surgery has become increasingly refined, safe, and effective, and provides a dramatic demonstration of the health benefits of weight loss. However, surgery is invasive, often comes with a steep short-term expense and is not scalable for the magnitude of the obesity problem, especially as the challenge has reached global proportions. Until recently, drugs approved for weight loss have lacked effectiveness, with most causing loss of just a few percent and little demonstration of lasting impact.

The last several decades have seen the discovery and delineation of the glucagon-like peptide 1 (GLP-1) system that has a physiologic role in glucose homeostasis. Development of drugs that activate the GLP-1 receptor (GLP-1R) has been a major addition to diabetes therapeutics. A serendipitous derivative of this work was the demonstration that GLP-1 reduces food intake and causes weight loss. There is now a series of solid clinical trials showing the utility of GLP-1R agonists (GLP-1RA) to treat obesity specifically, with effects that are significantly greater than with previous drugs, with promise to provide clinically meaningful weight reduction for a large percentage of those treated. This mini-review focuses on this new application of GLP-1RA.

The Scientific Rationale for Targeting the GLP-1 System for Weight Loss

In the mid-1990s, the discovery of leptin and its receptor were breakthroughs that merged the fields of metabolism and neuroscience, offering the most tangible promise yet of targeted treatment for weight loss. These captivating findings provided a tractable point of entry to connect systemic metabolism with brain regulation and launched a wave of investigation that led to rapid definition of key central nervous system (CNS) circuits controlling energy balance and nutrient homeostasis. Nearly lost in the torrent of activity around leptin were reports describing the effects of a then relatively esoteric peptide made in the intestine, glucagon-like peptide 1 (GLP-1), to reduce feeding when administered into the CNS of rodents (1). Looking back over 3 decades, the scientific importance of leptin, both as a physiological mediator and as the catalyst of a revolution in neuroscience, is inarguable. However, leptin never became the magic bullet for weight loss that early preclinical studies seemed to predict. Rather, it was the GLP-1 system, initially less compelling and informative about CNS function, that turned out to yield drugs with the potential to meaningfully affect body weight and the clinical correlates of obesity.

The key components of the GLP-1 system are the gastrointestinal (GI) tract, central and peripheral nervous systems, and the pancreatic islet (2). Expression of the preproglucagon gene is limited to specific enteroendocrine L-cells in the intestinal mucosa, a small population of hindbrain neurons,

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and α-cells of the pancreatic islet; GLP-1 is cleaved from proglucagon in each of these cell types. The GLP-1 receptor (GLP-1R) is expressed more diffusely, but the major loci for regulation of food intake are vagal afferent neurons, and neurons in the hypothalamus and hindbrain (3). Recent preclinical studies support a model whereby GLP-1 released in the gut mediates satiety through vagal nerve transmission (4), while activation of hindbrain neurons has a parallel, independent effect to suppress food intake (5). However, unlike the leptin receptor, deletion of the GLP-1R does not cause obesity in mice (6, 7), suggesting that this system may not be essential for normal body weight regulation. And although there are numerous sequence variants in the human GLP-1R gene, none of these have been definitively linked to body weight phenotypes (8).

While there remains a general view that GLP-1 released from the GI tract stimulates insulin secretion through an endocrine mechanism, there is only limited information that speaks to the effect of the endogenous peptide on feeding. Experimental evidence from human studies using functional magnetic resonance imaging (fMRI) is consistent with activation of the CNS by circulating GLP-1 from either exogenous or endogenous sources in a pattern compatible with satiety (9, 10). Similar findings suggest that the effects of plasma GLP-1 on the CNS are augmented in persons after bariatric surgery (11). Thus, while more work is required for confirmation and deeper mechanistic understanding, a case can be made that GLP-1 is an endocrine component of physiological satiety in humans.

Although preclinical studies suggest that the physiological role of GLP-1 in the regulation of satiety is auxiliary rather than essential, pharmacologic agonists of the GLP-1R invariably reduce food intake and body weight in both preclinical and human studies. Research volunteers treated with the GLP-1R agonist (GLP-1RA) exendin-4, the first GLP-1 analogue to be developed as a drug, consistently reported decreased appetite, reduced food intake, and weight loss with prolonged use. Similar findings were described in trials with other GLP-1RA, with consistent weight loss observed in subjects treated with exenatide, liraglutide, albiglutide, and dulaglutide. These pharmacologic agents reach much higher concentrations in the circulation than endogenous GLP-1, and their actions are likely to be mediated directly in the CNS. Based on preclinical studies, GLP-1RAs not only activate neurons in circumventricular organs accessible to the circulation, such as the median eminence in the midbrain and the area postrema in the hindbrain, but also reach key hypothalamic centers central to the regulation of feeding (12). Similar to studies of native GLP-1, exendin-4 also changes specific neural activity on fMRI images in patterns suggestive of satiety (13), and similar data have been obtained with other GLP-1RA. Taken together, a strong case can be made that pharmacologic GLP-1RAs have direct actions on the brain to suppress appetite and food intake.

The preponderance of clinical research related to GLP-1RAs has been directed toward the development and refinement of this class of agents for the treatment of type 2 diabetes (14). However, the consistent effects to reduce body weight in people with diabetes enrolled in clinical trials, as well as experimental evidence of mechanistic plausibility, established solid grounding to advance this class of drugs into trials specifically targeting weight loss in nondiabetic subjects. Over the last several years the results of these trials have been reported, and with them new hope for patients seeking to lose weight and reduce the health burdens of obesity.

Proof-of-Concept Clinical Trials of GLP-1RA for Weight Loss in Nondiabetic Humans

Exenatide, the commercial version of exendin-4, was approved by the Food and Drug Administration for the treatment of type 2 diabetes in 2005. Almost immediately it was used off-label for weight loss in people with and without diabetes, often with untested dosing regimens. However, formal studies of GLP-1RAs for weight loss were not published until 2009 (15, 16). The initial report described a group of nearly 600 volunteers with body mass index (BMI) 30 to 40 and nondiabetic glucose metabolism randomized to escalating doses of liraglutide, using orlistat or an injectable placebo as comparators. The 2 doses of liraglutide used in this trial (2.4 and 3.0 mg) were greater than what had been approved for treatment of diabetes. Over the course of 20 weeks of active treatment, there was dose-dependent weight loss in the liraglutide-treated subjects that was greater than either control group. Moreover, the GI symptoms that are the hallmark side effects of GLP-1RA— nausea, vomiting, and diarrhea in descending order of frequency—were generally well tolerated and comparable in amount and degree to what was seen in trials of these drugs for diabetes treatment; rates of nausea were dose-dependent but declined steadily over the first 10 weeks of treatment. A second study randomized 163 participants without diabetes and a mean BMI of ~ 40 to exenatide or placebo (PBO) in the context of a structured lifestyle intervention for 24 weeks. In this study a standard dose of exenatide caused loss of 5.1 kg from baseline compared to 1.6 kg with PBO, a significant difference that persisted for 1 month after cessation of treatment. Notably, the amount of weight loss in this relatively small study was at the higher end of the range for weight loss among subjects with diabetes in exenatide trials of glucose lowering. These 2 proof-of-concept studies, using liraglutide and exenatide, set the stage for longer trials that could provide a better estimate of clinical efficacy.

The first large, long-term study of a GLP-1RA for weight loss were the Satiety and Clinical Adiposity-Liraglutide Evidence trials, SCALE Obesity and Prediabetes (17), and SCALE Diabetes (18). The Obesity and Prediabetes trial was a multinational study testing the efficacy of 3.0 mg liraglutide in nondiabetic patients with a mean BMI of 38. After 56 weeks, patients in the liraglutide group had lost a mean of 8.4 kg of body weight compared to subjects randomized to PBO group who lost 2.8 kg. Almost all the subjects in the liraglutide group (92%) lost weight, and the numbers losing more than 5% and 10% of starting body weight was 3 times greater than among the placebo-treated subjects. In the SCALE Diabetes trial, which enrolled subjects with type 2 diabetes mellitus (T2DM), 3.0 mg of liraglutide led to 6.4 kg of weight loss compared to 2.2 kg with placebo, and 54% and 25% of subjects lost 5% or 10% of starting body weight. Adverse events in both trials, mostly gastrointestinal (GI), were similar to liraglutide trials for glucose lowering.

Clinical Trials With Semaglutide

Semaglutide is the most recent GLP-1RA to reach the clinic with approval in the United States in 2017. Similar to

liraglutide, semaglutide has a fatty acyl side chain that promotes binding to albumin, thus extending residence time in the circulation (19). However, the pharmacokinetics of the 2 drugs differ such that semaglutide has a much longer plasma half-life and is effective when given once weekly. In fact, in clinical trials of glycemic control, semaglutide was demonstrated to be more potent in lowering glycated hemoglobin (HbA1c) and body weight than liraglutide or dulaglutide (20, 21). Because of this, semaglutide was rapidly advanced into testing for weight loss in subjects without diabetes. The first of these studies was a comparison of multiple daily doses of semaglutide with liraglutide 3.0 mg in persons with BMI > 30 kg/m^2 (22). Doses of semaglutide ranging from 0.05 to 0.4 mg per day caused placebo-adjusted weight loss of 3.7% to 11.5%, and all but the lowest dose had greater effects than liraglutide (5.5%) over the 52 weeks of study. Adverse events were similar to what had been described for the many other studies of GLP-1RA.

The STEP (Semaglutide Treatment Effect in People with Obesity) program is a series of phase 3, randomized clinical trials of semaglutide for weight loss, targeting persons with BMI > 30. This program comprises 8 studies that include distinct groups of subjects or treatment regimens, all using subcutaneous semaglutide over a period of 68 weeks. Except for STEP 3, all trials included a similar lifestyle component consisting of 150 minutes per week of physical activity and a caloric reduced diet (500 kcal/day), and aside from STEP 2, the studies focused on weight loss in adults without diabetes; STEP 2 enrolled persons with BMI > 27 and type 2 diabetes. The primary outcomes for these studies followed standard outcome metrics for weight loss trials, with % of initial body weight lost relative to placebo, and % of subjects with 5% or 10% or greater weight loss as key outcome measures. Overall, the STEP trials published so far, trial numbers 1, 3, 4, and 8, enrolled more than 3700 nondiabetic subjects, of whom more than 75% were women and a similar percentage were Caucasian, with a mean age of 46 and a starting body weight of ~105 kg.

STEP 1 enrolled over 1900 adults who were assigned in a 2:1 ratio to semaglutide 2.4 mg weekly or PBO (23). While a diagnosis of diabetes excluded people from enrollment, 43% of the participants in STEP 1 had prediabetes and more than 75% had at least one comorbidity. Weight loss with semaglutide was greater than in the SCALE trials, with a mean change in body weight of 14.9% compared with 2.4% in the PBO group. More than 80% in the semaglutide group lost at least 5% of their body weight compared with 31% in PBO, 70% had weight loss of 10% or greater, and 30% had weight loss of at least 20%. Gastrointestinal side effects were more common with semaglutide than PBO, but most were transient and resolved without permanently discontinuing the regimen or prompting withdrawal from the study. Cholelithiasis occurred in 2.6% of participants receiving semaglutide and 1.2% of PBO subjects, and 3 participants given semaglutide had mild acute pancreatitis, 2 associated with gallstones; all recovered during the trial period. Based on these results, semaglutide seemed to be the most potent of the GLP-1RAs for weight loss, with mean PBO-corrected percentage weight loss roughly twice what had been reported for other drugs in this class. This inference was born out in STEP 8, a direct, within-trial comparison of semaglutide and liraglutide, in which mean weight loss was 15% and 6.5% respectively (24). STEP 1 was also the first evidence that a medical intervention could cause greater than 10% body weight loss in the majority of people treated.

In STEP 2, more than 1500 participants with T2DM were randomized 1:1:1 to weekly injections of semaglutide 2.4 mg, semaglutide 1.0 mg, or PBO for 68 weeks (25). Estimated changes in mean body weight among the 3 treatment arms were significant, −9.6% with 2.4 mg and −7% with 1.0 mg semaglutide, compared with −3.4% with PBO, and the side effect profile in this cohort did not differ from what was seen with semaglutide in STEP 1. Of note, the higher dose of semaglutide had an ~ 2.5% greater body weight loss than the lower dose, but with comparable glycemic lowering. Moreover, the lower mean reduction in body weight in people with diabetes compared to subjects without diabetes studied in STEP 1 (roughly 10% vs 15%) is consistent with the results seen in the SCALE trials, in which the nondiabetes group lost 8% and the diabetes cohort 5.4% with liraglutide treatment (18, 25). While both trials with T2DM subjects had cohorts that were older, with a larger percentage of males, and distinct medication use compared to the studies of nondiabetic subjects, this trend in the magnitude of effect of GLP-1RA on body weight seems consistent and is worth testing further.

STEP 3 randomized 611 nondiabetic subjects to semaglutide 2.4 mg or PBO as adjuncts to intensive behavioral therapy with a structured diet (26). All participants were given a low-calorie meal replacement diet for the first 8 weeks of the study, and intensive behavioral therapy across the entire 68-week protocol. Participants were also prescribed 100 minutes of physical activity per week, which was increased by 25 minutes every 4 weeks for a maximum of 200 minutes per week. At week 68, the estimated mean body weight change was −16.0% for semaglutide compared to −5.7% for PBO, with a difference of 10.3%. Similar to other STEP trials, a majority, 75.3%, of participants given semaglutide achieved weight loss of at least 10%. The relatively high rate of weight loss in the PBO group, 27.0% of whom lost at least 10% of starting body weight, attests to the intensity of the lifestyle intervention. However, the 16% body weight change with semaglutide in STEP3 does not differ very much from the results seen with semaglutide in STEP 1, which leaves open the question of how much intensive lifestyle modification adds to a potent drug effect.

STEP 4 was designed to test the effect of withdrawal of semaglutide after a course of weight loss therapy to assess effects on weight maintenance (27). A total of 803 subjects received the 2.4 mg dose of semaglutide for 20 weeks and lost ~ 10% of starting body weight. Of these, 535 were subsequently randomized to continue semaglutide, while 286 were given a weekly PBO over the following 48 weeks. During the 20-week run-in, subjects had reductions in waist circumference, BMI, blood pressure, HbA1c, and improvements in lipid profiles associated with weight loss. After randomization, mean weight was reduced a further −7.9% in the semaglutide cohort, while those switched to PBO regained more than half of their initial weight loss. There was also reversal of improved obesity-associated comorbidities, such as blood pressure, in the discontinuation arm. The mean 68-week weight loss in the continuously treated cohort in STEP 4 of more than 17%, with 40% of treated subjects losing more than 20% of initial body weight, was the largest in the STEP program. However, the results of this trial indicate that beneficial effects of semaglutide on body weight seem to require maintenance of treatment.

Overall, the STEP trials are the best demonstration to date of the potential for medical weight loss. Semaglutide had effects on weight loss that significantly outstrip other agents currently available, with benefits on clinically meaningful correlates of obesity such as blood pressure, lipid profiles, and glycemia. The effects of semaglutide on weight loss did not wane over the 68-week study durations and longer trials would be necessary to determine the ultimate course of weight loss. It is not clear from STEP4 whether people taking a shorter course of therapy would return to their starting body weight over time, although experience with other weight loss interventions suggests that this would be the case. A summary of the completed and ongoing STEP trials is presented in Table 1. An orally available form of semaglutide has been studied extensively in subjects with type 2 diabetes and has resulted in weight loss that is comparable to the injectable form when corrected for exposure to circulating drug (28).

GLP-1RA and Weight Loss in Special Populations

Obesity in children and adolescents is one of the major health care concerns in pediatrics, and dietary and other lifestyle measures have had limited impact when pitted against the omnipresent environmental influences that promote positive energy balance in young people. In a recent trial, 250 adolescents with BMI > 30 were randomized to liraglutide or PBO for a 56-week comparison (29). While only 80% of the group given liraglutide were able to titrate to the top dose of 3 mg, there was a significant reduction in body weight, ~ 6% placebo-corrected, with active treatment. Roughly 40% of the subjects in the liraglutide group lost more than 5% of starting BMI compared with 19% of PBO controls. These results are in keeping with the results of liraglutide trials in adults and suggest that young people respond to GLP-1RAs comparably. Effective treatment of obesity in young people is likely to have a disproportionate impact on public health because of their increased exposure to the health consequences of increased body weight.

Despite the effect of bariatric surgery to improve a range of metabolic parameters for people with T2DM and/or obesity, about half of treated patients do not reach diabetes remission or a BMI < 30 over 5 years (30). Additionally, 21% to 43% of those who do achieve remission of type 2 diabetes after bypass surgery relapse within 3 to 9 years (31). To meet the needs of these patients, GLP-1RA therapy has been assessed in people with gastric bypass or sleeve gastrectomy. In the GRAVITAS trial, 80 people with previous bariatric surgery and persistent diabetes were randomized to liraglutide 1.8 mg or PBO for 26 weeks (32). Treatment with liraglutide caused a reduction of 1.22% in HbA1c compared with PBO. Moreover, subjects receiving liraglutide lost ~ 5 kg more weight than the controls (32). These findings are somewhat surprising because people with bariatric surgery have endogenous GLP-1 levels that are 10 to 20 times greater than normal. In fact, increased signaling through the GLP-1R system is a common explanation as to how gastric bypass and sleeve gastrectomy produce metabolic benefit. However, plasma concentrations of GLP-1RAs exceed circulating levels of native GLP-1 by at least 100-fold, and clinical responses to GLP-1RA are proportional to drug exposure (28). Moreover, the elevated GLP-1 concentrations after bariatric surgery are transient, occurring only after meals; long-acting GLP-1RAs cause persistent exposure of the GLP-1R to stimulation.

Implications, Unanswered Questions, and Future Directions

The completion of most of the STEP trials has demonstrated the potential for a GLP-1RA as a weight management option and has implications for the physiology and pharmacology of GLP-1RAs as well as for their clinical utility. From a physiological standpoint, it appears that there is considerable excess capacity in the GLP-1R signaling system. Concentrations of endogenous GLP-1 appear to act at the very bottom of an exposure-response curve that has not yet had a maximal boundary for weight loss defined. This raises the possibility that continued refinement of GLP-1RAs, particularly modifications that can decrease the common GI side effects, would allow further dose escalation and even greater efficacy. From a pharmacologic standpoint, the application of GLP-1RA to weight loss is now the most common form of therapeutic CNS-endocrinology, with a pharmacologic ligand directed at the brain as the primary target. It seems likely that pharmacokinetics contributes to the weight loss effect of these drugs, with longer, steadier exposure having greater effects. However, it is curious that liraglutide is not as potent as semaglutide given the similarities in molecular size and the receptor-binding moieties of these agents and the comparable concentrations the drugs reach in the circulation (28, 33). Understanding whether subtle differences in structure affect access to key brain sites, or interaction with the GLP-1R would be useful in continuing development of GLP-1RAs and other incretin-based agents.

Table 1. Summary of the STEP trials.

Trial	Subjects	# enrolled	Design	Published
STEP 1	ND/ MN	1961	Sema 2.4/PBO	Ref 23
STEP 2	T2DM/ MN	1210	Sema 2.4/1.0/PBO	Ref 25
STEP 3	ND	611	Sema 2.4/PBO + intensive lifestyle	Ref 26
STEP 4	ND	902	Sema 2.4 run-in with switch to PBO or continued Sema	Ref 27
STEP 5	ND	304	Sema 2.4/PBO for 104 weeks	Completed
STEP 6	ND/ Japan, S Korea	40	Sema 2.4/Sema 1.7	Completed
STEP 7	ND/ China, S Korea, Brazil	375	Sema 2.4/PBO	Ongoing
STEP 8	ND	338	Sema 2.4/Lira 3.0	Ref 24

Doses of semaglutide and liraglutide are in milligrams (mg).
Abbreviations: ND, nondiabetic; T2DM, type 2 diabetes; MN, multinational; Sema, semaglutide; PBO, placebo; Lira, liraglutide.

From a clinical standpoint, the development of GLP-1RA for weight loss, and particularly the magnitude of the effects in the STEP trials, provides a much-needed ray of hope for patients and their providers. The effects of semaglutide treatment over 2 years, with average weight loss of 10% to 20%, is a significant step forward in what can be achieved with drug therapy of obesity. The efficacy of medications in clinical trials often reflects their optimal performance, and it will be important to evaluate the effectiveness of semaglutide and related drugs in the broader scope of clinical practice. Moreover, the subjects who comprised the STEP program were predominantly white and female, and how the results translate to a more diverse population is still to be determined. Given the continued weight loss from 68 to 104 weeks shown in STEP 4, it is important to know what longer treatment periods will look like. Some level of weight regain is seen with other GLP-1RAs on treatment longer than 1 year, and this is the tendency in patients with bariatric surgery as well. Finally, all the GLP-1RAs are expensive and near-term cost will reduce widespread access; cost has been shown to be a factor in nonadherence with this class of drug (34). In this regard, understanding fixed and modifiable patient characteristics and behaviors that affect efficacy will allow better allocation of health care resources.

Beyond demonstrating the direct clinical benefits of semaglutide, the STEP trials exemplify the potency of GLP-1R agonism for weight loss. This has provided added impetus to an already vibrant area of pharmaceutical research. It is plausible that even longer-acting formulations can be developed that improve convenience and adherence. Moreover, recent research in the structure and function of the GLP-1R and other G-protein coupled receptors suggests that modifications of ligand-receptor interactions can shift downstream signaling and the relative action to toxicity balance. Combined therapy is also under development. Co-injection of an amylin agonist with semaglutide caused 17% greater weight loss over 20 weeks than 2.4 mg semaglutide alone (35). And advances in peptide chemistry have led to the development of multireceptor agonists that may have enhanced potency for metabolic effects. For example, the dual GLP-1R/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist tirzepatide has demonstrated effects on weight loss that are roughly twice that seen with 1.0 mg of semaglutide (36). Other dual agonists that activate the GLP-1R and glucagon receptor (GcgR), or tri-agonists that signal through GLP-1R/GIPR/GcgR, have shown promise in preclinical studies and are under investigation in humans. These interesting results suggest that harnessing the activity of the GLP-1R may be just the beginning of a breakthrough to scalable, meaningful, and lasting treatment of obesity. In that sense the STEP program may represent only a first step.

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Disclosures

D.A.D. consults for Eli Lilly and Sun Pharmaceuticals. N.K. has nothing to disclose.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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